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No. 06-1249

IN THE
Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

ON WRIT OF CERTIORARI TO
THE VERMONT SUPREME COURT

REPLY BRIEF FOR PETITIONER

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CORPORATE DISCLOSURE STATEMENT

Petitioner Wyeth has no parent corporation, and no publicly held company owns 10% or more of its stock.

TABLE OF CONTENTS

Page

CORPORATE DISCLOSURE STATEMENT i

TABLE OF AUTHORITIES iii

ARGUMENT 3

I. WYETH COULD NOT COMPLY WITH BOTH STATE AND FEDERAL LABELING DUTIES 3

A. Federal Law Generally Prohibits Unilateral Changes To FDA-Approved Labeling 4

B. The CBE Exception Did Not Permit Wyeth To Eliminate IV Push From Phenergan's Labeling 7

C. Respondent's Remaining Arguments Fail To Show That Wyeth Could Comply With Both State And Federal Law 11

II. ENFORCEMENT OF THE STATE-LAW DUTY INVOKED BY RESPONDENT WOULD OBSTRUCT THE PURPOSES OF THE FDCA AND FDA'S REGULATIONS 13

A. The Jury Directly Contradicted FDA's Judgment About What Phenergan's Labeling Should Say About IV Administration (Including IV Push) 14

B. Respondent's Arguments About Congressional Intent Fail 20

III. THE COURT SHOULD DECIDE THIS CASE—NOT THE OTHER SCENARIOS RESPONDENT AND HER AMICI ADVANCE 25

CONCLUSION 28

TABLE OF AUTHORITIES

CASES

Page(s)

Arkansas Louisiana Gas Co. v. *Hall*, 453 U.S. 571 (1981) 12

Auer v. *Robbins*, 519 U.S. 452 (1997) 8

Bates v. *Dow Agrosciences LLC*, 544 U.S. 431 (2005) 11, 21, 24

Bine v. *Sterling Drug, Inc.*, 422 S.W.2d 623 (Mo. 1968) 22

Buckman Co. v. *Plaintiffs' Legal Committee*, 531 U.S. 341 (2001) 12

Colacicco v. *Apotex Inc.*, 521 F.3d 253 (3d Cir. 2008) 12

Crosby v. *National Foreign Trade Council*, 530 U.S. 363 (2000) 24

Dowhal v. *Smithkline Beecham Consumer Healthcare*, 88 P.3d 1 (Cal. 2004) 12

Fidelity Federal Savings & Loan Ass'n v. *de la Cuesta*, 458 U.S. 141 (1982) 11, 19

Fisher v. *Golladay*, 38 Mo. App. 531 (1889) 22

Freightliner Corp. v. *Myrick*, 514 U.S. 280 (1995) 21

Geier v. *American Honda Motor Co.*, 529 U.S. 861 (2000) 11, 18, 19, 20, 21

Heckler v. *Chaney*, 470 U.S. 821 (1985) 8

International Paper Co. v. *Ouellette*, 479 U.S. 481 (1987) 25

TABLE OF AUTHORITIES—Continued

Page(s)

McEwen v. *Ortho Pharmaceutical Corp.*, 528 P.2d 522 (Or. 1974) 22

Medtronic, Inc. v. *Lohr*, 518 U.S. 470 (1996) 11, 18, 20, 24

Moehlenbrock v. *Parke, Davis & Co.*, 169 N.W. 541 (Minn. 1918) 22

Riegel v. *Medtronic, Inc.*, 128 S. Ct. 999 (2008) 5, 11, 18, 21, 22

Roginsky v. *Richardson-Merrell, Inc.*, 378 F.2d 832 (2d Cir. 1967) 22

Sprietsma v. *Mercury Marine*, 537 U.S. 51 (2002) 11, 18

Thomas v. *Winchester*, 6 N.Y. 397 (1852) 22

United States v. *Chemical Foundation, Inc.*, 272 U.S. 1 (1926) 15

Werner v. *Upjohn Co.*, 628 F.2d 848 (4th Cir. 1980) 9

STATUTES, REGULATIONS, AND LEGISLATIVE MATERIALS

Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301 *et seq.*

§ 331(d) 5

§ 355(a) 5, 25

§ 355(b)(1)(F) 5

§ 355(d) 15, 19, 26

§ 355(d)(1) 5

TABLE OF AUTHORITIES—Continued

Page(s)

§ 355(d)(2) 5

§ 355(d)(4) 5

§ 355(d)(5) 5

§ 355(d)(7) 5

§ 355(k) 22

§ 360k(a) 21

21 C.F.R.

§ 201.80(e) 9

§ 310.3(h)(5) 6

§ 314.70(b)(1) 7

§ 314.70(b)(2)(v) 4, 7

§ 314.70(b)(3) 4, 7

§ 314.70(c)(6)(iii) 7

§ 314.70(d)(2)(ix) 7

§ 314.70(d)(2)(x) 7

§ 314.80 22

§ 314.105(b) 26

§ 314.110 26

30 Fed. Reg. 993 (Jan. 30, 1965) 8

47 Fed. Reg. 46,622 (Oct. 19, 1982) 8

50 Fed. Reg. 7452 (Feb. 22, 1985) 6

71 Fed. Reg. 3922 (Jan. 24, 2006) 5, 6, 20

73 Fed. Reg. 2848 (Jan. 16, 2008) 6

TABLE OF AUTHORITIES—Continued

Page(s)

73 Fed. Reg. 49,603 (Aug. 22, 2008) 8, 9, 10

H.R. 6110, 73d Cong. (1933) 23

Pub. L. No. 105-115, 111 Stat. 2296 (codified at 21 U.S.C. § 356a) 4

OTHER AUTHORITIES

Hager, Donald L., & James N. Wilson, *Gangrene of the Hand Following Intra-Arterial Injection*, 94 Arch. Surg. 86 (1967) 17

Miller, R., et al., *Intra-Arterial Injection of a Barbiturate—A Case Report*, 23 Anesthesia Progress 25 (1976) 17

Webb, Gilbert A., & Nelson Lampert, *Accidental Arterial Injections*, 101 Am. J. Obst. & Gynec. 365 (1968) 17

Zimmerman, Joseph F., *Preemption in the U.S. Federal System*, 23 Publius: J. of Federalism 1 (1993) 21, 22

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Conflict preemption operates by force of the Constitution itself, and the conflict here is manifest. Fulfilling its mandate under the FDCA, FDA concluded that Phenergan was safe and effective for use under the conditions described in the approved labeling. That labeling included specific cautionary language directed to "IV push." Under the circumstances presented here, the FDCA and its implementing regulations prohibited Wyeth from changing that labeling without FDA's prior approval. But a jury applying Vermont law concluded that Wyeth was *required* to change the Phenergan labeling to contraindicate a method of administration that FDA had approved, based on a weighing of risk and benefit different from FDA's. The jury's application of Vermont law and FDA's expert administra-

tion of federal law are thus in direct conflict. None of the sources respondent invokes to divine congressional intent diminishes that conclusion.

To distract from that point, respondent claims that FDA never actually considered the risks of IV push, and that the jury's verdict therefore did not directly second-guess any judgment or command FDA actually made. That contention is both legally irrelevant and factually wrong. It is legally irrelevant because the FDCA requires FDA to consider the risks and benefits of all conditions of use, including methods of administration, presented in a New Drug Application (NDA). Respondent has not suggested that FDA was not *informed* about the risks of IV (or IV push) administration of Phenergan; to the contrary, her theory has always been that FDA simply made a wrong judgment despite having that information. FDA should be presumed, however, to have examined in good faith all information it possessed relevant to its approval decision. Requiring (or allowing) litigants to probe whether FDA focused on a precise piece of information or possible labeling variation would be unworkable and would impose a significant burden on the agency.

The contention is also factually wrong because FDA was fully aware of the harm that could result from exposure of arterial blood to Phenergan, and considered the particular risks posed by IV administration of Phenergan, including IV push. That is why FDA repeatedly directed Wyeth to include prominent warnings that IV administration required "extreme care," or "gangrene requiring amputation" would "likely" follow. These warnings, and the many instructions aimed at reducing the risk of arterial exposure, represented FDA's considered judgment of how the labeling should address the risk at issue in this case, and FDA reached

that judgment with full attention to all methods of IV administration. There is therefore no room for respondent to argue that the jury's conclusion does not contradict that of FDA.

Obscuring that patent conflict, respondent and a chorus of amici treat this case as though it were about something else—a case in which a drug manufacturer concealed risk information from FDA, or in which material information about a drug's risks emerged after FDA approved the drug and its labeling. Whatever might be said about preemption in those situations, they are most definitely not this case. Respondent never argued that Wyeth concealed information from FDA, and never contended that Wyeth should have changed its labeling to reflect information that came to light after its labeling was approved. Respondent tried *this* case on the theory that FDA had the pertinent information but reached the wrong conclusion, and that the jury should set FDA right. In this situation, state tort law is undoubtedly preempted.

ARGUMENT

I. WYETH COULD NOT COMPLY WITH BOTH STATE AND FEDERAL LABELING DUTIES

In general, federal law prohibits changes to drug labeling unless a manufacturer obtains prior FDA approval of a supplemental New Drug Application (sNDA). That prohibition is inherent in the FDCA itself: the hallmark of the Act is the requirement of prior approval by an expert agency that balances the safety and efficacy of new drugs according to the conditions of use comprehended by their labeling, and labeling is FDA's principal tool for striking that balance. Thus, FDA's final approval in 1998 of Wyeth's sNDA for Phenergan was conditioned on Wyeth's making specific

changes to the labeling, and FDA instructed Wyeth that the final printed labeling "must be identical" to the wording in the approved application. JA 382; *see also* JA 356-365. Were there any doubt concerning the FDCA's prohibition on unilateral labeling changes, FDA has resolved it by explicitly prohibiting them, with only narrow exceptions. 21 C.F.R. § 314.70(b)(2)(v)(A), (b)(3). Under that regulation, Wyeth could have changed Phenergan's labeling only through the CBE exception. That exception permitted no change in this case.

A. Federal Law Generally Prohibits Unilateral Changes To FDA-Approved Labeling

Respondent contends (Br. 21-22, 32-36) that the FDCA broadly allows manufacturers to make unilateral changes to the labeling of an approved drug without obtaining FDA approval, subject only to the statutory prohibition against distributing "misbranded" drugs. That is incorrect. The statute's text recognizes no exception to the prior-approval requirement that would permit manufacturers to distribute drugs with labeling that deviates from the FDA-approved language.[1] And the structure of the Act—independent of the prohibition on "misbranding"—is incompatible with allowing manufacturers to make unilateral labeling changes.

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[1] Notably, when Congress wished to allow manufacturers to make unilateral changes in the *manufacturing* process of an approved drug (also a component of the NDA), it expressed that intent by amending the FDCA specifically to allow such deviations from the NDA. *See* Pub. L. No. 105-115, § 116(a), 111 Stat. 2296, 2313-2315 (codified at 21 U.S.C. § 356a).

The innovation of the 1938 FDCA was to augment previously existing federal prohibitions on adulteration and misbranding with a comprehensive pre-marketing approval scheme. The FDCA as amended prohibits distribution of a new drug unless an application approved by FDA is effective with respect to that drug. 21 U.S.C. § 355(a); *see also id.* § 331(d). The labeling to be used for the drug is a central component of that application, *id.* § 355(b)(1)(F), and must be approved before the application becomes effective, *id.* § 355(d)(7). FDA's review of the safety and efficacy of the drug focuses on "the conditions prescribed, recommended, or suggested in the proposed labeling." *Id.* § 355(d)(1), (2), (4), (5). Approved labeling is therefore inseparable from FDA's approval of the drug itself. *See* 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006). As this Court held in the analogous context of pre-marketing approval of medical devices, where FDA's safety and effectiveness determination is based on the terms of the application as approved, it follows that the approved product must be marketed "with almost no deviations from the specifications in [that] application." *Riegel* v. *Medtronic, Inc.*, 128 S. Ct. 999, 1007 (2008).

Respondent concedes (Br. 35-36) that at least some labeling changes could render the drug a "new drug" for which no approved application is effective and would therefore be prohibited by the statute. Respondent nevertheless argues that labeling changes intended to add or strengthen warnings or (as here) to withdraw uses or methods of administration would not result in a new drug and may therefore be made unilaterally, subject only to the statutory prohibition against misbranding. That too is incorrect. "[S]ubstantive changes in labeling … are more likely than other changes to affect the agency's previous conclusions

about the safety and effectiveness of the drug." 50 Fed. Reg. 7452, 7470 (Feb. 22, 1985). For that reason, FDA has provided that many kinds of labeling changes—including changes to methods of administration—may render a drug a "new drug" requiring new approval. 21 C.F.R. § 310.3(h)(5).[2]

Under respondent's contrary view, Wyeth could have changed Phenergan's labeling to contraindicate any form of administration it wished without seeking FDA's approval. Her theory would extend even to unilateral contraindication of *intramuscular* injection, even though doing so would directly contradict FDA's judgment that deep IM injection is the preferred route of administration, JA 391, and would affect the safety of the drug by leaving no option other than the IV route. FDA was required to make, and did make, a determination about the balance between safety and efficacy with respect to *all* approved methods of administration. Any change unilaterally contraindicating one of those methods can undermine the balance Congress intended FDA to strike. That is why federal law with only limited exceptions precludes manufacturers from making such changes without FDA approval.[3]

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[2] Respondent reasons (Br. 37) that because Wyeth could have withdrawn Phenergan from the market altogether, it must have had the lesser power to withdraw a method of administration from Phenergan's labeling. That ignores the nature of a licensing regime: a licensee may choose not to exercise its license at all, but it cannot exercise that license without regard to its terms and conditions.

[3] Citing extra-record material, respondent's amici assert that manufacturers frequently make unilateral changes to drug labeling without FDA taking any enforcement action. But as FDA has explained, in practice manufacturers routinely consult with FDA

To the extent the FDCA leaves room for manufacturers to make any unilateral labeling changes, FDA long ago made clear that as a general rule, labeling changes may be made only with FDA's prior approval. 21 C.F.R. § 314.70(b)(1), (b)(2)(v)(A), (b)(3). The only exceptions are minor or editorial changes that do not affect drug safety or efficacy, *id.* § 314.70(d)(2)(ix), (x), and CBE changes that require FDA approval but may be implemented upon submission of a supplemental application, *id.* § 314.70(c)(6)(iii). Respondent does not claim these regulations rest on an unreasonable reading of the FDCA or are otherwise invalid. Wyeth could therefore have changed the Phenergan labeling after FDA approved its sNDA in 1998 only if a change would have been permissible under the CBE exception. It would not have been.

B. The CBE Exception Did Not Permit Wyeth To Eliminate IV Push From Phenergan's Labeling

The CBE exception allows manufacturers to make labeling changes before FDA acts on an sNDA only

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before changing risk information on labeling. 71 Fed. Reg. at 3934; 73 Fed. Reg. 2848, 2849 (Jan. 16, 2008). Since manufacturers rarely act unilaterally in implementing labeling changes, it is no surprise FDA rarely has to take enforcement action against them for doing so.

Moreover, the cited examples cannot be taken at face value. One brief, for example, contends that Wyeth unilaterally added a warning to the labeling of its drug Effexor, based on no new information and with no negative enforcement consequences from FDA. *See* Witczak Amicus Br. 5-8. That is wrong. Wyeth submitted the proposed warning to FDA in a CBE supplement, citing new developments in the industry's understanding of risks associated with drugs like Effexor. FDA considered the change and rejected it, instructing Wyeth to use a different warning.

when necessary "to correct concerns about newly discovered risks from the use of the drug." 47 Fed. Reg. 46,622, 46,623 (Oct. 19, 1982); *see also* U.S. Br. 22-23 (June 2, 2008). As demonstrated in Wyeth's opening brief (at 35-39), the CBE regulation reflects FDA's discretionary decision to forbear from taking enforcement action against distribution of a drug with labeling that differs from that approved in the NDA.

FDA introduced the CBE exception in 1965 as an incremental change to a regime that otherwise permitted no labeling changes at all without prior approval, *see* Pet. Br. 35-37, so that new information or conclusions about drug safety could be "placed into effect at the earliest possible time." 30 Fed. Reg. 993, 993 (Jan. 30, 1965). Refinements in 1982 retained the prior-approval requirement for all labeling changes except minor editorial revisions and changes made "to correct concerns about newly discovered risks from the use of the drug" and to "make available important new information about the safe use of a drug product." 47 Fed. Reg. at 46,623, 46,635. And FDA recently amended the CBE again to codify its "longstanding view" that CBE changes are appropriate "only to reflect newly acquired information," and "only if there is sufficient evidence of a causal association" between the drug and the risk at issue. 73 Fed. Reg. 49,603, 49,603, 49,604 (Aug. 22, 2008); *see also id.* at 49,608 (amendment did not effect a "substantive policy change" or "alter the agency's current practices").

FDA's interpretation of its own regulation is entitled to deference, *see Auer* v. *Robbins*, 519 U.S. 452, 461 (1997), particularly here, where the regulation reflects FDA's exercise of its substantial discretion to enforce the statute, *see* 30 Fed. Reg. at 994; *see also Heckler* v. *Chaney*, 470 U.S. 821, 835 (1985). As FDA has

explained, the CBE exception must be construed narrowly because FDA's "comprehensive scientific evaluation of the product's risks and benefits … is embodied in the labeling for the product[.]" 73 Fed. Reg. at 49,604.

Respondent (Br. 8) cites another FDA regulation requiring manufacturers to revise drug labeling "as soon as there is reasonable evidence of an association of a serious hazard with a drug." 21 C.F.R. § 201.80(e). That regulation does not support a broader reading of the CBE exception. Nothing in section 201.80(e) suggests that the required revisions should be made without FDA's approval. Section 201.80(e) states a substantive standard for labeling changes; it does not create an alternative procedure for making them. And because section 201.80(e) requires labeling changes "as soon as" evidence of a hazard emerges, that regulation too is directed to new safety information. Reading section 201.80(e) to require unilateral labeling changes would render the CBE exception a nullity—for in respondent's view, the CBE exception would simply permit what section 201.80(e) already required.[4]

Under the proper construction of the CBE exception, Wyeth had no good-faith basis to implement a CBE change. Respondent never alleged that Wyeth

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[4] Respondent (Br. 8 n.5) cites *Werner* v. *Upjohn Co.*, 628 F.2d 848 (4th Cir. 1980), for the claim that FDA's regulations encourage unilateral action by manufacturers to improve warnings, but that court did not address whether such changes would be appropriate when the change did not reflect new safety information. To the contrary, the court explained that FDA regulations allow labeling changes without prior approval "where new side effects are discovered by the company." *Id.* at 859.

had information about the risks of Phenergan it did not disclose to FDA. Rather, respondent's theory of liability has been that Phenergan's labeling failed to foreclose a method of administration that carried a risk of which Wyeth and FDA were both aware when FDA approved that labeling. *See infra* pp. 16-18. And while FDA's recent regulation provides that "newly acquired information" can include new analyses of old information previously submitted to FDA, so long as it reveals a risk of a "different type or greater severity or frequency than previously included in submissions to FDA," 73 Fed. Reg. at 49,604, respondent did not claim that any such new analysis came to light between FDA's approval of Phenergan's labeling in 1998 and respondent's injury in 2000.[5] Because no CBE change was permissible, federal law prohibited Wyeth from changing the Phenergan labeling that FDA instructed it to use.[6]

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[5] Respondent's amicus, while claiming that "analyses might have revealed the extent of the dangers posed by Phenergan"—apparently referring to the very dangers the labeling already warned of—rests that contention on extra-record studies and reports published years after respondent's treatment with Phenergan. *See* Budhwani Amicus Br. 18; *see also id.* at 15-23. The brief suggests no reason why Wyeth should have reached a different conclusion in 2000 about Phenergan's risks than FDA had reached when it approved the labeling in 1998.

[6] Respondent questions (Br. 18-19, 43 n.29) whether Wyeth adequately raised below its argument that the CBE regulation permits only labeling changes based on new safety information. But Wyeth advanced that construction before the Vermont Supreme Court, *see* Wyeth Br. 13-14, 24 (Vt. Nov. 22, 2004), which rejected it, *see* Pet. App. 11a, 13a. Moreover, interpretation of the CBE exception—and the question of preemption—are questions of law, so there was no reason to argue them to the jury or to object

C. Respondent's Remaining Arguments Fail To Show That Wyeth Could Comply With Both State And Federal Law

Respondent contends (Br. 43-45) that Wyeth could have complied with both federal and state law simply by paying respondent's money judgment, without changing Phenergan's labeling. But this Court has made clear that "common-law liability is premised on the existence of a legal duty, and a tort judgment therefore establishes that the defendant has violated a state-law obligation." *Riegel*, 128 S. Ct. at 1008 (quotation marks omitted); *see also Medtronic, Inc.* v. *Lohr*, 518 U.S. 470, 504 (1996) (Breyer, J., concurring in part and concurring in the judgment). State tort law is therefore subject to preemption every bit as much as positive enactments of state law. *See, e.g.*, *Bates* v. *Dow Agrosciences LLC*, 544 U.S. 431, 443 (2005); *Geier* v. *American Honda Motor Co.*, 529 U.S. 861, 881 (2000). That conclusion certainly applies to "impossibility" conflict preemption, which asks whether "compliance" with both state and federal law is impossible. *E.g.*, *Fidelity Fed. Sav. & Loan Ass'n* v. *de la Cuesta*, 458 U.S. 141, 153 (1982). As the Court has held, state law is preempted where it is "impossible to comply with [federal] regulation *without incurring liability* under state common law." *Sprietsma* v. *Mercury Marine*, 537 U.S. 51, 65 (2002) (emphasis added).

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to particular jury instructions. And in light of respondent's own contention at trial that Wyeth and FDA were fully aware of the relevant risks, *see infra* pp. 17-18, no remand is required to assess whether the evidence would have supported a labeling change under the CBE exception as interpreted by FDA (*cf.* Resp. Br. 43 n.29).

Respondent alternatively contends (Br. 37) that Wyeth could have filed a supplemental application proposing to contraindicate IV push and implemented the change upon FDA approval. But there is no reason to assume FDA would have approved a hypothetical proposed change, and it is unworkable for that counterfactual inquiry to be the touchstone of the preemption analysis. FDA does not approve all proposed labeling changes. *See, e.g.*, JA 271, 359; *see also Colacicco* v. *Apotex Inc.*, 521 F.3d 253, 269-271 (3d Cir. 2008); *Dowhal* v. *Smithkline Beecham Consumer Healthcare*, 88 P.3d 1, 4-6 (Cal. 2004). Respondent's theory would inappropriately assign to juries the speculative task of determining whether and when FDA would have approved a particular hypothetical labeling change. This Court has disapproved similar undertakings. *See Arkansas La. Gas Co.* v. *Hall*, 453 U.S. 571, 578-579, 580-581 (1981); *Buckman Co.* v. *Plaintiffs' Legal Comm.*, 531 U.S. 341, 354 (2001) (Stevens, J., concurring in the judgment). And in any event, on the record here, Wyeth had no new information unknown to FDA that could have been the basis of a supplemental NDA.[7]

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[7] Moreover, respondent offers no reason to believe that merely submitting a proposed change to FDA would discharge Wyeth's purported state-law duty. As respondent herself has explained, "the state-law duty imposed … here is premised on the label's failure to have proper warnings or instructions regarding IV-push administration," Resp. Br. 52 n.37 (emphasis omitted), not on any failure to propose that change. The suggestion advanced by some of respondent's amici that Wyeth could have issued a "Dear Doctor" letter is similarly irrelevant; respondent's theory of liability was premised on "the *label's* failure to have proper warnings or instructions." *Id.* (emphasis added); *see also* JA 17 (¶ 17).

II. ENFORCEMENT OF THE STATE-LAW DUTY INVOKED BY RESPONDENT WOULD OBSTRUCT THE PURPOSES OF THE FDCA AND FDA'S REGULATIONS

Congress intended that drug-labeling approval decisions be made by an agency that makes expert scientific judgments, balancing safety and efficacy to benefit overall public health. In approving Wyeth's sNDA in 1998, FDA concluded that the benefits of Phenergan outweighed its risks under all conditions of use comprehended by the labeling, including administration by IV push. Yet under state law, a jury was permitted to decide that the same drug was *not* safe and effective under the approved labeling. By directly contradicting FDA's judgment, the jury's enforcement of state law conflicted with and frustrated the objectives of federal law.[8]

Respondent attempts to evade this conflict by asserting, first, that FDA made no judgment balancing the risks and benefits of IV push, so that the jury's verdict did not contradict FDA's approval of Phenergan's labeling. Respondent further argues that Congress did not intend to preempt common-law remedies, which are said to complement FDA regulation and serve the same objectives. These arguments fail.

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[8] Respondent has wisely abandoned the Vermont Supreme Court's reasoning that section 202 of the 1962 Drug Amendments precludes application of "obstacle" preemption to cases under the FDCA. Resp. Br. 54 n.40.

A. The Jury Directly Contradicted FDA's Judgment About What Phenergan's Labeling Should Say About IV Administration (Including IV Push)

At trial, respondent's counsel expressly exhorted the jury to override FDA's judgment: "The FDA doesn't make the decision, you do." JA 212. In this Court, respondent contends (*e.g.*, Br. 1, 16, 47-48) that no rational person could find—as FDA did—that the benefits of IV push ever outweigh its risks.[9] Those arguments underscore what respondent's suit is really about: second-guessing FDA's judgment about the relative risks and benefits of IV administration and how those risks should be managed and communicated by the drug's labeling. The Phenergan labeling in place when respondent was injured was the language FDA approved and directed Wyeth to use. FDA made that approval decision based on the information available about the risks of IV administration, including IV-push injection. The state-law duty respondent seeks to enforce was a duty to use different labeling based on the

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[9] Both the physician assistant and the attending physician testified that IV-push injection was appropriate because earlier intramuscular injection had been ineffective, and faster delivery of a higher concentration was needed because Phenergan was being given in combination with IV-push Demerol. JA 40-41, 60-61, 104-106. (Respondent never argued Demerol should not have been given by push.) While the evidence was mixed whether IV drip is as risk-free as respondent suggests, *see* JA 67, 75, it is clear that drip delivers lower concentrations at slower rates, and therefore would not have achieved the benefits respondent needed and IV push offered (when performed correctly). *See, e.g.*, JA 187. The PA thus explained that she chose push over drip because she needed to treat respondent "in a swift and timely way," JA 106, 109, and that she had done so effectively for years, JA 104-105; Tr. 69 (Mar. 12, 2004). *See also* Pet. Br. 19 n.10, 22 n.11.

view that FDA got it wrong—a clear conflict between state and federal law.

Respondent seeks to avoid that conclusion by arguing that in this case, the jury and FDA did not reach judgments about the same thing. Whereas the jury found Phenergan's labeling to be inadequate specifically with respect to IV push, respondent contends, FDA considered only IV administration generally and made no determination regarding IV push. That contention does not withstand scrutiny.

First, FDA was required by statute to evaluate Phenergan's safety and efficacy under all conditions of use comprehended by the labeling and to find the labeling adequate to permit safe use before approving the drug. 21 U.S.C. § 355(d). The labeled conditions of use directly addressed IV administration, including by IV push. Consistent with its statutory mandate, FDA must therefore be presumed to have made a judgment about the risks and benefits of IV push before approving Phenergan for distribution with that labeling. *Cf. United States* v. *Chemical Found., Inc.*, 272 U.S. 1, 14-15 (1926) ("The presumption of regularity supports the official acts of public officers, and, in the absence of clear evidence to the contrary, courts presume that they have properly discharged their official duties.").

Second, whether or not the jury's verdict actually reflected a judgment about IV push, rather than IV generally—a matter on which the record is unclear[10]—

[10] Respondent's primary claim at trial was that the Phenergan labeling should have contraindicated all IV administration; warning against IV push was a second-best alternative advanced by some of her witnesses. JA 31-32, 36, 59, 63, 65, 79-81, 83, 211. Neither the jury instructions nor the verdict form required the

it is entirely clear that FDA made a judgment about IV push. Several of the instructions for IV administration on the labeling that FDA reviewed and approved are applicable *only* to injection by IV push.[11] Furthermore, the record of meetings and correspondence between Wyeth and FDA regarding Phenergan's labeling shows FDA considered IV push.[12] FDA's 1987 letter to Wyeth cited twenty medical journal articles it had reviewed that discuss intra-arterial injection. JA 313-315.

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jury to make any finding specific to IV push. JA 220, 225-226. Whichever theory the jury accepted contradicted FDA's judgment. That respondent was permitted to present both arguments underscores the broad scope of the conflict.

[11] JA 390-391. Respondent's physician explained at trial that the labeling's recommended rate of administration (not to exceed 25 mg per minute) refers to "IV push, as opposed to say being in a bag and dripped over a couple of hours." JA 52. The labeling's reference to "plungers" and "rigid needles" likewise suggests injection by IV push: "by talking plungers and rigid needles, that's the way you do it, to push it with the plunger." JA 53. He further explained that aspiration, which is also discussed in the labeling, is a step in the process of IV push. JA 47-48. The labeling also gives instructions for use of the Tubex Injector—a single-use cartridge and reusable plastic injector with a rigid plunger used to administer a single dose of Phenergan by IV push injection. JA 107, 391.

[12] For example, at the 1976 Advisory Committee meeting addressing proposed revisions to the labeling, a question arose regarding the difficulty of aspiration and detection of arterial pressure using the Tubex Injector instead of a "plain needle and syringe." JA 294. These references to aspiration, use of the Tubex, and use of a needle and syringe relate only to IV push. Similarly, in a 1987 letter to Wyeth, FDA suggested enhanced safety could be achieved using a "running intravenous" system. JA 312. (A "running IV" is the same thing as "IV drip." JA 15-16.) FDA thus considered not only the risks associated with IV push, but also the possibility that IV drip might provide a safer alternative.

Those articles confirm that the danger FDA was concerned about was caused by IV push.[13] FDA was thus focused on a risk associated specifically with IV push and was aware of the differences between IV push and IV drip.[14] Indeed, if, as respondent contends (Br. 1), IV drip poses "virtually no risk," then the risks and adverse events FDA considered and addressed on the labeling could *only* have concerned IV push.

Consistent with this record, respondent's witnesses testified that FDA knew the risks of IV administration of Phenergan, including IV push. One of respondent's experts testified that "FDA knew about the risks" that were the subject of respondent's claims, had discussed those risks in correspondence with Wyeth, and had received relevant adverse event reports. JA 97. Another of respondent's experts agreed that the reports FDA received discussed cases where Phenergan caused amputation as a result of "direct injection … not any other

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[13] Several articles reported on cases in which patients suffered serious injury, including gangrene requiring amputation, as a result of IV injections of Phenergan or other drugs administered by IV push. *See, e.g.*, Webb & Lampert, *Accidental Arterial Injections*, 101 Am. J. Obst. & Gynec. 365, 366 (1968); Hager & Wilson, *Gangrene of the Hand Following Intra-Arterial Injection*, 94 Arch. Surg. 86, 86 (1967); Miller et al., *Intra-Arterial Injection of a Barbiturate—A Case Report*, 23 Anesthesia Progress 25, 26 (1976). One cited article even discussed the relative safety of IV drip compared to IV push but noted that IV drip may sometimes be impractical. Webb & Lampert, at 371.

[14] No court below found that FDA was unaware of the risks of IV push or the differences between push and drip. The statements cited by respondent (Br. 19-20, 51-52) speak only to the supposed lack of evidence showing why FDA rejected the labeling change Wyeth proposed in 1988 or whether FDA would have rejected all such warnings.

method of injection." JA 74; *see also* Tr. 222-225 (Mar. 8, 2004) (testifying about FDA's awareness of several cases of injury caused by direct IV injection).

Respondent (Br. 53 & n.38) analogizes this case to *Sprietsma* and *Lohr*, but it actually mirrors *Geier*, where the agency made a specific judgment that balanced competing considerations to promote its ultimate safety objective. In that situation, this Court concluded that a state-law tort duty that would have upset that regulatory balance could not stand. *See* 529 U.S. at 864-865, 874-881. In *Sprietsma*, by contrast, the Coast Guard had no statutory duty to regulate propeller guards, and accordingly made no decision regarding their desirability; thus, a tort suit enforcing a state-law judgment that propeller guards were necessary interfered with no federal judgments or objectives. *See* 537 U.S. at 61-62, 65-68. Likewise, as this Court explained in *Riegel*, the "substantial equivalence" review at issue in *Lohr* did not require FDA to conduct (and FDA did not conduct) any safety and efficacy review of the medical device at issue, and the regulatory scheme imposed no product-specific requirements. *See Riegel*, 128 S. Ct. at 1006-1007. In contrast, FDA pre-approval of drugs—like its review of the medical devices at issue in *Riegel*—is a rigorous, individualized process under which FDA approves every new drug, and Congress permits the distribution of those drugs solely under the terms of the approved application. *Id.* at 1004-1005, 1007.

Allowing a lay jury to countermand FDA's expert determination about how drug labeling should communicate a drug's risks and benefits frustrates the statu-

tory and regulatory scheme.[15] Respondent contends (Br. 51) that no conflict exists because when it comes to labeling, FDA does not balance risks and benefits. But FDA is bound by statute to balance a drug's safety and efficacy, and drug labeling is integral to that balance. 21 U.S.C. § 355(d). A drug FDA views as sufficiently beneficial to warrant approval despite its risks under certain labeled conditions might not provide the same net benefit if the conditions of use on the labeling were altered. FDA's judgment that the labeling it approves strikes the best balance in light of the information it has reviewed and is the *correct* standard—not a *minimum* standard—is entitled to significant weight, for FDA is best positioned to assess whether and how conflicting state labeling requirements would affect drug

[15] That conflict would exist even if respondent were correct that the CBE regulation would have permitted Wyeth to implement a unilateral labeling change without any new information about the risks of IV push. It would be one thing for federal law (as respondent would read it) to allow a manufacturer to make an interim labeling change while asking FDA to reconsider its own previous judgment through an sNDA; it would be quite another for a state jury to compel a manufacturer to make a change based on the State's entirely separate, and conflicting, judgment about the propriety of the labeling. The FDCA is concerned not just with the content of drug labeling, but also with who shall make those labeling decisions. A state regime that *required* a manufacturer to implement a labeling change that federal law would merely permit it to implement temporarily while awaiting FDA's reconsideration would undermine FDA's approval authority and clash with the FDCA regulatory regime. The Court reached a similar conclusion in *Geier*: in that case, nothing in federal law prohibited manufacturers from installing airbags, yet a state law *requiring* the use of airbags still conflicted with federal law. *See* 529 U.S. at 878-879, 881; *see also de la Cuesta*, 458 U.S. at 155.

safety and efficacy. *See* 71 Fed. Reg. at 3934-3935; *see also Geier*, 529 U.S. at 883; *Lohr*, 518 U.S. at 496.[16]

B. Respondent's Arguments About Congressional Intent Fail

Respondent argues that Congress could not have intended to preempt common-law liability because the FDCA contains no express preemption clause; Congress was presumably aware of common-law tort suits involving drugs; and the FDCA and state-law duties serve the same purpose of protecting consumers. These arguments all fail.

First, although respondent invokes congressional intent, she misapprehends the intent that is pertinent here. Wyeth does not argue that Congress intended to occupy the field of pharmaceutical safety; nor does it contend that Congress intended to preempt all common-law liability for unsafe drugs. Indeed, conflict preemption does not depend on any showing that Congress ever focused on the question of common-law liability. Rather, the relevant intent is Congress's judgment that drug-labeling decisions should be made

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[16] FDA also balances competing interests to prevent manufacturers from including excessive or unsubstantiated information on labeling. 71 Fed. Reg. at 3922, 3935. Several of respondent's amici contend that the prospect of "overwarning" is illusory because it rarely occurs. But that is precisely the point. FDA oversight prevents overwarning; if manufacturers had unlimited discretion to make labeling changes without approval and could face tort liability for failing to do so, the risk of overwarning—and of deterring beneficial uses of drugs—would increase. Overwarning would also make it harder for health-care providers to locate important information on the labeling and to be confident that all information on the labeling is based on scientific evidence.

by an expert agency that balances risks and benefits and that FDA's labeling judgments should be binding on drug manufacturers. Any state-law duty that interferes with the accomplishment of those objectives is preempted under standard preemption doctrine.

The absence of an express preemption clause in the FDCA is neither dispositive nor even particularly revealing. Conflict preemption arises directly from the Supremacy Clause: where state and federal law cannot be reconciled, the Constitution requires that the state law give way. For this reason, the Court has repeatedly held that neither the absence of express preemption language nor the inclusion of express language with a limited preemptive scope forecloses preemption that arises from an actual conflict between federal and state law. *See, e.g.*, *Freightliner Corp.* v. *Myrick*, 514 U.S. 280, 287-289 (1995); *see also Geier*, 529 U.S. at 869, 884.

The express clause in the MDA, on which respondent and her amici rely, serves a different purpose than the implied preemption rule that governs here. The MDA clause expressly preempts state-law requirements that are "different from, or *in addition to*" federal requirements. 21 U.S.C. § 360k(a) (emphasis added). The clause thus preempts non-parallel state-law requirements without any showing of actual conflict. *See Riegel*, 128 S. Ct. at 1011; *see also Bates*, 544 U.S. at 447-448, 452-454 (applying similar language). Comparing the FDCA and MDA is of limited help also because express preemption clauses are largely a modern phenomenon. *See* Zimmerman, *Preemption in the U.S. Federal System*, 23 Publius: J. Federalism 1, 1-2, 4, 6 (1993). Express preemption clauses were rare when Congress passed the FDCA in 1938, but had become much more common by the time Congress adopted the

MDA in 1976. *Id.* at 1-2. Moreover, the proliferation of state regulation of medical devices created a need for a broader preemptive scope in the MDA. *See Riegel*, 128 S. Ct. at 1003. No comparable pattern of state regulation of drugs had emerged when Congress enacted the FDCA in 1938.

Respondent and her amici invoke the history of common-law liability for failure to warn, but most of the cases they cite would not be affected by a finding of preemption here. Several of the cases involve liability for selling drugs that were adulterated or incorrectly identified and would thus have violated the FDCA. *See, e.g.*, *Thomas* v. *Winchester*, 6 N.Y. 397 (1852); *Fisher* v. *Golladay*, 38 Mo. App. 531 (1889); *Moehlenbrock* v. *Parke, Davis & Co.*, 169 N.W. 541 (Minn. 1918). Others involved drug labeling that failed to reflect emerging risk information the manufacturer learned of but failed to disclose. *See, e.g.*, *Bine* v. *Sterling Drug, Inc.*, 422 S.W.2d 623 (Mo. 1968); *McEwen* v. *Ortho Pharm. Corp.*, 528 P.2d 522 (Or. 1974); *Roginsky* v. *Richardson-Merrell, Inc.*, 378 F.2d 832 (2d Cir. 1967). Unlike here, the defendants in many of these cases were held liable for conduct that had not been approved by FDA or that otherwise violated federal law (which requires manufacturers promptly to disclose new safety information to FDA, *see* 21 U.S.C. § 355(k); 21 C.F.R. § 314.80). To be sure, under the principles articulated here, preemption might result in some of the cases respondent and her amici cite; but in most of those cases, a finding of preemption would have to be premised on a theory different from the one Wyeth has put forward.

The legislative history cited by respondent establishes nothing useful about congressional intent in this case. Respondent notes (Br. 4) the absence of a private

right of action in the 1938 Act that had been included in a 1933 precursor to the FDCA. But the 1933 bill would have provided a right of action for damages "caused by a violation of this Act." H.R. 6110, 73d Cong. § 25 (1933). That provision thus envisioned that *federal* law would set the relevant standard of conduct. It says nothing about Congress's intent to preserve tort suits against conduct that, like Wyeth's conduct here, does not violate the FDCA. Moreover, the 1933 version of the bill did not include the pre-approval system that was ultimately adopted in 1938. The conclusion of certain legislators that no private right of action was required in the 1933 bill therefore sheds no light on Congress's preemptive intent with respect to drug labeling that has undergone the pre-market approval process.

Respondent also cites (Br. 28-29) legislative measures from 1995 and 1997 that referred to drug manufacturer "liability" under state law. But Wyeth does not contend that the FDCA and FDA's regulations preempt all tort liability against drug manufacturers. It is therefore not significant that Congress has occasionally indicated that some tort liability would continue to coexist with federal regulation. Respondent also cites 2007 legislation that enhanced FDA's authority to order post-approval labeling changes, but preserved manufacturers' responsibility "'to maintain … label[s] in accordance with existing requirements, including [the CBE regulation].'" Resp. Br. 38 (quoting 121 Stat. 925-926). That language preserved only requirements under federal law, and it is silent on what Congress believed those "existing requirements" entail. The language is therefore neutral on the meaning of the CBE exception and on the preemption question before the Court. *See* U.S. Br. 32-33.

Citing *Bates* and *Lohr*, respondent finally contends (Br. 45-46) that no conflict exists because both the FDCA and the Vermont-law duty to warn serve the same purpose: to protect consumers and safeguard public health. But safety is not the FDCA's sole objective. All drugs are unsafe in at least some circumstances, particularly when they might be administered incorrectly. The FDCA requires FDA to strike a balance between safety and efficacy by identifying and managing acceptable levels of risk with respect to particular drugs while also promoting availability of beneficial drugs.

By contrast, *Bates* involved a regulatory scheme in which EPA had waived all efficacy review and made no individualized determination about the labeling statements that the plaintiff's suit challenged. 544 U.S. at 440. EPA was not required, therefore, to balance consumer protection and the public health more generally in the manner that FDA must under the FDCA. Likewise, in *Lohr*, "substantial equivalence" review under the MDA required no particularized balancing of safety and effectiveness. 518 U.S. at 478-479, 493-494. Moreover, it was not the common purposes underlying state and federal law that led the Court to see no preemption in *Bates* and *Lohr*, but rather that the specific state-law duties at issue were parallel to the duties imposed by federal law. *See Bates*, 544 U.S. at 444-452; *Lohr*, 518 U.S. at 493-494, 495, 501. (Indeed, in *Bates*, the Court held that state-law labeling requirements that were not equivalent to federal requirements *would* be preempted. 544 U.S. at 452-454.) Where, as here, federal and state law impose conflicting duties, no consonance of purpose—even if it existed—could eliminate that conflict and preclude operation of the Supremacy Clause. *See Crosby* v. *National Foreign Trade Coun-*

cil, 530 U.S. 363, 379 (2000); *International Paper Co.* v. *Ouellette*, 479 U.S. 481, 494 (1987).[17]

III. THE COURT SHOULD DECIDE THIS CASE—NOT THE OTHER SCENARIOS RESPONDENT AND HER AMICI ADVANCE

Respondent's amici devote great energy to arguing that state-law tort suits should not be preempted because FDA lacks sufficient resources to monitor the safety of drugs after they (and their labeling) have been approved. Whether or not that criticism of FDA is correct—and many of amici's arguments cannot be taken at face value[18]—it is irrelevant in this case. Respondent never argued that Wyeth violated its state-law duty by concealing information from FDA or failing to change the Phenergan labeling to reflect safety information that came to its attention *after* FDA approved the labeling that was in effect when respondent was injured. Rather, respondent argued that FDA had information about the risk to which she was exposed but nonetheless made a regulatory decision that, in her

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[17] Vermont's regulatory compliance defense does not resolve the conflict. While the FDCA makes FDA approval conclusive, 21 U.S.C. § 355(a), the regulatory compliance defense does not: FDA's judgment is just one opinion the jury is free to accept or reject. *See, e.g.*, JA 216. That is not parallel to federal law.

[18] Amici's arguments rest largely on extra-record material that does not tell the whole story. For example, the brief of certain editors and authors of the *New England Journal of Medicine* (at 13-18) distorts the facts surrounding the marketing and withdrawal of Wyeth's diet drugs Pondimin and Redux. While a rejoinder to such attacks is well beyond the scope of this case and the record, their account of Wyeth's conduct in connection with those drugs is quite incorrect.

view, did not adequately protect the public from that risk.

The criticism (*e.g.*, Resp. Br. 11) that prior to 2007 FDA lacked authority to initiate labeling changes after a drug was approved is similarly irrelevant here. Whatever the limits on FDA's ability to demand labeling changes on its own initiative after it has approved a drug application, FDA certainly has authority to compel labeling changes when reviewing an NDA or sNDA by withholding approval until its demands are met. 21 U.S.C. § 355(d); 21 C.F.R. §§ 314.105(b), 314.110. That is all this case is about, and FDA exercised that authority in reviewing and approving several supplemental NDAs for Phenergan after its initial approval in 1955.[19] Indeed, FDA conditioned its 1998 approval of the Phenergan labeling in place when respondent was injured on Wyeth's implementing specific changes and distributing the drug with labeling "identical" to the FDA-approved language. JA 382; *see also* JA 356-365.

A preemption holding here will not necessarily resolve a tort suit where a manufacturer withheld safety information from FDA or learned of new safety information after FDA approved the drug's labeling. Indeed, the concern raised by these arguments is pre-

[19] Respondent is incorrect to suggest that Wyeth disregarded FDA's labeling requests. Wyeth added all the labeling information FDA directed it to add concerning the risk of intra-arterial injection. *Compare* JA 282, 283, 285 *with* JA 351-352. In the only instance respondent cites (Br. 11) in which Wyeth allegedly did not follow FDA's instructions—which did not concern arterial exposure—Wyeth's initial disagreement was referred to an outside advisory committee, which reviewed the issue and concluded that a warning should indeed be added. JA 290-291. Wyeth added that warning. *Compare* JA 291 *with* JA 324.

cisely the concern that is addressed by FDA's interpretation of the CBE regulation and its recent revision. If a manufacturer learns of new information or draws a new conclusion about a drug's safety after FDA approval and fails to disclose that information to FDA or to reflect it in an appropriate labeling change when permitted to do so under the CBE rule, that manufacturer might not have a preemption defense to tort liability. Preemption in the circumstances of this case thus provides an incentive for manufacturers to bring new information to FDA's attention and update the labeling as soon as it comes to light.

In short, respondent and her amici are quite wrong to suggest that preemption in this case would displace all common-law remedies for injured patients. Common-law remedies may remain, for example, for injuries caused by violations of federal law. But the Supremacy Clause requires that the substantive standard of conduct that is enforced by a tort remedy be consistent with federal law. No matter its purposes or benefits, tort law cannot be said to complement federal regulation when it imposes a state-law duty that contradicts manufacturers' federal obligations and FDA's labeling approval judgments. Where those circumstances do not exist, there might be no conflict between state and federal law, and a tort remedy might be available. But where, as here, a state tort judgment would frustrate Congress's intent by challenging FDA's labeling approval judgment, that state judgment cannot stand under the Supremacy Clause.

CONCLUSION

The judgment of the Vermont Supreme Court should be reversed.

Respectfully submitted.

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